impede hematopoiesis and by itself has no prognostic significance. In approximately 15% of patients, however, myelofibrosis is accompanied by significant extramedullary hematopoiesis, hepatosplenomegaly, and transfusion-dependent anemia, which are manifestations of stem cell failure. The organomegaly can cause significant mechanical discomfort, portal hypertension, and progressive cachexia. Although the incidence of acute nonlymphocytic leukemia is increased in PV, the incidence of acute leukemia in patients not exposed to chemotherapy or radiation therapy is low. Interestingly, chemotherapy, including hydroxyurea, has been associated with acute leukemia in *JAK2* V617F–negative stem cells in some PV patients. *Erythromelalgia* is a curious syndrome of unknown etiology associated with thrombocytosis, primarily involving the lower extremities and usually manifested by erythema, warmth, and pain of the affected appendage and occasionally digital infarction. It occurs with a variable frequency and is usually responsive to salicylates. Some of the central nervous system symptoms observed in patients with PV, such as ocular migraine, appear to represent a variant of erythromelalgia.

Left uncontrolled, erythrocytosis can lead to thrombosis involving vital organs such as the liver, heart, brain, or lungs. Patients with massive splenomegaly are particularly prone to thrombotic events because the associated increase in plasma volume masks the true extent of the red cell mass elevation measured by the hematocrit or hemoglobin level. A "normal" hematocrit or hemoglobin level in a PV patient with massive splenomegaly should be considered indicative of an elevated red cell mass until proven otherwise.

TREATMENT POLYCYTHEMIA VERA

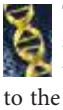
PV is generally an indolent disorder, the clinical course of which is measured in decades, and its management should reflect its tempo. Thrombosis due to erythrocytosis is the most significant complication and often the presenting manifestation, and maintenance of the hemoglobin level at ≤140 g/L (14 g/dL; hematocrit <45%) in men and ≤120 g/L (12 g/dL; hematocrit <42%) in women is mandatory to avoid thrombotic complications. Phlebotomy serves initially to reduce hyperviscosity by bringing the red cell mass into the normal range while further expanding the plasma volume. Periodic phlebotomies thereafter serve to maintain the red cell mass within the normal range and to induce a state of iron deficiency that prevents an accelerated reexpansion of the red cell mass. In most PV patients, once an iron-deficient state is achieved, phlebotomy is usually only required at 3-month intervals. Neither phlebotomy nor iron deficiency increases the platelet count relative to the effect of the disease itself, and thrombocytosis is not correlated with thrombosis in PV, in contrast to the strong correlation between erythrocytosis and thrombosis in this disease. The use of salicylates as a tonic against thrombosis in PV patients is not only potentially harmful if the red cell mass is not controlled by phlebotomy, but is also an unproven remedy. Anticoagulants are only indicated when a thrombosis has occurred and can be difficult to monitor if the red cell mass is substantially elevated owing to the artifactual imbalance between the test tube anticoagulant and plasma that occurs when blood from these patients is assayed for prothrombin or partial thromboplastin activity. Asymptomatic hyperuricemia (<10 mg/dL) requires no therapy, but allopurinol should be administered to avoid further elevation of the uric acid when chemotherapy is used to reduce splenomegaly or leukocytosis or to treat pruritus. Generalized pruritus intractable to antihistamines or antidepressants such as doxepin can be a major problem in PV; interferon α (IFN-α), psoralens with ultraviolet light in the A range (PUVA) therapy, and hydroxyurea are other methods of palliation. Asymptomatic thrombocytosis requires no therapy unless the platelet count is sufficiently high to cause bleeding due an acquired form of von Willebrand's disease in which there is adsorption and proteolysis of high-molecular-weight von Willebrand factor (VWF) multimers by the expanded platelet mass. Symptomatic splenomegaly can be treated with pegylated IFN-α. Pegylated IFN-α can also produce complete hematologic and molecular remissions in PV, and its role in this disorder is currently under investigation. Anagrelide, a phosphodiesterase inhibitor, can reduce the platelet count and, if tolerated, is preferable to hydroxyurea because it lacks marrow toxicity and is protective against venous thrombosis. A reduction in platelet number may be necessary for the treatment of erythromelalgia or ocular migraine if salicylates are not effective or if the platelet count is sufficiently high to increase the risk of hemorrhage but only to the degree that symptoms are alleviated. Alkylating agents and radioactive sodium phosphate (^{32}P) are leukemogenic in PV, and their use should be avoided. If a cytotoxic agent must be used, hydroxyurea is preferred, but this drug does not prevent either thrombosis or myelofibrosis in PV, is itself leukemogenic, and should be used for as short a time as possible. Previously, PV patients with massive splenomegaly unresponsive to reduction by chemotherapy or interferon required splenectomy. However, with the introduction of the nonspecific JAK2 inhibitor ruxolitinib, it has been possible in the majority of patients with PV complicated by myelofibrosis and myeloid metaplasia to reduce spleen size while at the same time alleviating constitutional symptoms to due to cytokine release. This drug is currently undergoing clinical trials in PV patients intolerant of hydroxyurea. In some patients with end-stage disease, pulmonary hypertension may develop due to fibrosis or extramedullary hematopoiesis. A role for allogeneic bone marrow transplantation in PV has not been defined.

Most patients with PV can live long lives without functional impairment when their red cell mass is effectively managed with phlebotomy alone. Chemotherapy is never indicated to control the red cell mass unless venous access is inadequate.

PRIMARY MYELOFIBROSIS

Chronic PMF (other designations include *idiopathic myelofibrosis*, *agnogenic myeloid metaplasia*, or *myelofibrosis with myeloid metaplasia*) is a clonal disorder of a multipotent hematopoietic progenitor cell of unknown etiology characterized by marrow fibrosis, extramedullary hematopoiesis, and splenomegaly. PMF is the least common chronic MPN, and establishing this diagnosis in the absence of a specific clonal marker is difficult because myelofibrosis and splenomegaly are also features of both PV and CML. Furthermore, myelofibrosis and splenomegaly also occur in a variety of benign and malignant disorders (Table 131-3), many of which are amenable to specific therapies not effective in PMF. In contrast to the other chronic MPNs and so-called acute or malignant myelofibrosis, which can occur at any age, PMF primarily afflicts men in their sixth decade or later.

ETIOLOGY



The etiology of PMF is unknown. Nonrandom chromosome abnormalities such as 9p, 20q−, 13q−, trisomy 8 or 9, or partial trisomy 1q are common, but no cytogenetic abnormality specific to the disease has been identified. *JAK2* V617F is present in approximately 50% of PMF patients, and mutations in the thrombopoietin receptor *Mpl* occur in about 5%. Most of the rest have mutations in the

TABLE 131-3 DISORDERS CAUSING MYELOFIBROSIS

Malignant	Nonmalignant
Acute leukemia (lymphocytic, myelogenous, megakaryocytic)	HIV infection
Chronic myeloid leukemia	Hyperparathyroidism
Hairy cell leukemia	Renal osteodystrophy
Hodgkin's disease	Systemic lupus erythematosus
Primary myelofibrosis	Tuberculosis
Lymphoma	Vitamin D deficiency
Multiple myeloma	Thorium dioxide exposure
Myelodysplasia	Gray platelet syndrome
Metastatic carcinoma	
Polycythemia vera	
Systemic mastocytosis	